Original Article

# Impact of Zingiber Officinale on Symptoms and Hormonal Changes During the Menopausal Period – A Clinical Trial in Duhok, Iraq

**Niroosh H. Taha[1], Kawa F. Dizaye[2]**

[1]Department of Pharmacology, College of Pharmacy - University of Duhok, Iraq
[2]Department of Basic Sciences, College of Medicine - Hawler Medical University, Erbil, Iraq. Email: kawa.dizaye@hmu.edu.krd
Note: This study has been registered on ClinicalTrials.gov under NCT Identifier: NCT05499793) Clinical Trial on Menopause: Zingiber Officinale powder, Placebo - Clinical Trials Registry - ICH GCP
Corresponding Email: niroosh.taha@uod.ac

## Abstract

**Background:** The women's quality of life changes dramatically after 45 years due to the tremendous physiological changes. These changes end with menopause; however, years preceding this time are frustrating for many women because up to 20% of women might experience several symptoms of variable intensity affecting their quality of life. In Duhok city, Zingiber officinale is used as a traditional medicine by menopausal women to alleviate some menopausal symptoms. Therefore, this study was designed to examine the impact of Zingiber officinalis on menopausal symptoms and their relation to female sex hormonal changes in middle-aged women in Duhok city. **Subjects and Methods:** A randomized clinical trial was conducted for twelve weeks on fifty menopausal women. Thirty women were treated daily with Zingiber officinale (1000 mg), and the other twenty women were given starch as a placebo (1000 mg). Blood samples were taken from both groups before and after twelve weeks to assess the serum levels of female sex hormones. In addition, the menopausal rating scale was used to measure the frequency and intensity of menopausal symptoms. **Results:** The most common menopausal symptoms among studied women were physical symptoms (54%), like hot flashes, night sweating and musculoskeletal pain. Zingiber officinale significantly reduced the intensity of menopausal symptoms with a significant increase in serum estrogen levels ($p < 0.001$). In addition, significant reduction in serum level of FSH was also observed ($p < 0.001$). **Conclusion:** Elevation of serum estrogen levels and reduction in FSH by ginger powder are helpful in reducing the intensity of menopausal symptoms.

Keywords: Menopause, Menopausal symptoms, Zingiber officinale, Sex hormones, clinical trial.

## Introduction

Menopause is inevitable and irreversible end of menstruation caused by ovarian malfunction.[1] It naturally occurs as part of the aging processes in the female life cycle, with a mean age of 51 years.[2] However, premature menopause may occur much earlier when triggered by medical therapy or surgical removal of both ovaries in younger women.[3] In most cases, females' lives substantially change, particularly in the years approaching menopause, due to a steady loss in ovarian function after 45 years. This transitional period is clinically known as climacteric or perimenopause.[4] Women during this period often suffer from physical and mental disturbances. These symptoms may begin a couple of years before the cessation of menstruation.[5] In addition, gradual ovarian dysfunction may cause vasomotor, psychological and urogenital symptoms.[6] However, women report varying frequency and intensity of these symptoms which may be related to ethnicity, lifestyle, social and economic status, psychological state of the women and attitude towards menopause.

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**Address for Correspondence:** Department of Pharmacology, College of Pharmacy - University of Duhok, Iraq
Email: niroosh.taha@uod.ac

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Generally, these symptoms are mild and transient in more than two-third of women. However, some women might suffer from severe symptoms for longer time.[7]

The hormonal alteration during the perimenopausal period is complex and varies widely amongst individuals.The expected alterations include significant fluctuations in estradiol levels and a considerable decrease in inhibin B and progesterone plasma levels. Furthermore, the level of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) remain elevated due to a negative feedback mechanism imposed by low estrogen and inhibin B in the blood. Meanwhile, ovarian sensitivity to FSH and LH is significantly reduced.[6]

The goal of menopausal symptom therapy is not only to relieve early unpleasant menopausal symptoms, like hot flashes, night sweating, musculoskeletal pain, and depression, but also to reduce the long-term side effects of medication by individualizing the treatment.[8] Although hormonal treatment for menopausal symptoms is the most effective method to alleviate vasomotor symptoms worldwide,[9] yet, the adverse effects of estrogen outweigh its potential benefits. Therefore, use of systemic estrogens to treat these symptoms have declined dramatically.[10]

An alternative treatment might be helpful when hormonal therapy is unsafe, as in women with thromboembolic disease or certain hormone-dependent malignancies. This includes non-hormonal and non-pharmacological therapies[11] such as phytoestrogens which are among the most crucial non-pharmacological treatments used to modulate physiological and pathological processes related to menopausal syndromes and bone remodeling.[12] Zingiber officinale (ginger) is a traditional folk medicinal herb used worldwide for over 2000 years to alleviate many illnesses like diabetes, high blood pressure, cancer and other conditions.[13] Several active ingredients of ginger own a significant role in treating multiple human diseases. Ginger's pharmacological benefits are generally linked to these active biological constituents which may have anti-inflammatory, immunomodulatory, antioxidant and anti-diabetic properties.[14] They may also have estrogen-like effects; therefore, they might be used to treat menopausal symptoms.[12]

This study aims to highlight the effects of Zingiber officinale on female menopausal symptoms and their relation to female sex hormone changes in the blood during perimenopausal and menopausal period in middle-aged women in Duhok city, Iraq.

# Methodology

## Ethical Approval

After taking scientific and ethical approval from the College of the Pharmacy, University of Duhok and the Directorate of Duhok Health (reference number: 24102021-10-36), a double-blind clinical interventional study was launched at the Gynecology Department in Azadi Teaching Hospital in Duhok city, Iraq, from December 2021 to June 2022.

## Study Subjects

This study was designed to assess the impact of Zingiber officinale on menopausal symptoms in women between 45 and 60 years and their relation to sex hormone changes**.** Initially, this study recruited seventy women who matched the inclusion criteria i.e. symptomatic women between 45 and 60 years of age who did not receive any treatment for their symptoms and had no chronic diseases, coagulopathies or hormone-dependent malignancies. All the recruited women were informed about the study protocols. After taking written consent, they were randomly divided into two groups through a random number generator software. A professional pharmacist was responsible for delivering the treatment to them and neither the researchers nor the participants were aware of the type of treatment given. Thirty-five women were placed in control group and were given starch powder as placebo (500mg/capsule) twice daily for twelve weeks. The starch powder was purchased from the local market and formulated to look similar to the ginger capsule. The other thirty-five women were given Zingiber officinale powder (500mg/capsule) twice daily for twelve weeks. These capsules were purchased from Pure Mountain Botanicals, 1712 Pioneer Ave # 1139 Cheyenne Wyoming 82001 (USA). Twenty women in the placebo group, while thirty women in the ginger group completed the survey. Remaining participants didn't finish the research survey because they were either noncompliant with the treatment or were missed during the study period, hence, they were excluded.

## Data Collection

Direct face-to-face interviews were conducted using a predesigned questionnaire form to collect data. Blood samples were collected before and after twelve weeks of the treatment. The datasheet was separated into two sections: the first had the sociodemographic information and BMI estimate of the participants and the second had the frequency and intensity of menopausal symptoms. These symptoms were assessed using an internationally recognized questionnaire menopausal rating scale (MRS), an officially validated scale based on the quality of life instrument standards.[15] The eleven elements of MRS were divided into three categories i.e. physical, psychological and urogenital. The physical symptoms included hot flashes, night sweating, heart pain, sleeping problems and muscle and joint problems whilepsychological manifestations included depressive mood, irritability, anxiety and mental exhaustion. Likewise, the urogenital symptoms included sexual problems, bladder problems and vaginal dryness. The English version of the MRS was used

in the study, however, because some participants could not speak English, a well-trained, qualified professional nurse administered the questionnaire in the local language before and after the treatment. Patients who answered mild and moderate were grouped as one, and those who responded severe to very severe were also grouped while calculating the prevalence. This grouping was done to eliminate any bias while choosing the best response. The MRS total score ranges from zero (asymptomatic) to forty-four (the highest degree of complaints). According to literature, total score of ≤ 11was regarded as asymptomatic, a score from 12 to 35 was considered mild to moderately severe, while score >35 was assessed as a severe manifestation.[16]

## Measurement of Hormonal Levels

The serum estrogen, progesterone, FSH, and LH levels were measured before and after treatment with Cobas e 411 analyzers (Roche Diagnostics). The kits used for each hormone include: estradiol III [Test number: 1370], progesterone III [Test number: 1370], elecsys FSH [Test number: 150] and elecsys [Test number: 140].

## Statistical Analysis

The statistical calculations were performed by JMP pro 14.3.0. The general and medical information of the participants in both groups were presented as mean ± SD or percentage (%). Similar pattern was followed for the prevalence of menopausal symptoms. On the other hand, general characteristics of both groups were compared using an independent t-test or Pearsons chi-squared test. Likewise, the comparison of hormonal changes between the groups at baseline and between pre and post-treatment was done through independent and paired t-test, respectively. The prevalence of menopausal symptoms among participants was tested using Pearsons chi-squared test. In addition, the incidence rate of menopausal symptoms beforte and after treatment in both groups was compared using McNemar test. The uncertainty of difference between pre and post-treatment was determined at 95% confidence interval (CI) and a p-value of less than 0.05 was considered statistically significant.

## Results

As shown in Figure 1; the most common menopausal symptoms among the studied women were physical symptoms (54%), followed by urogenital (33%) and psychological symptoms (13%). However, no significant differences were reported between the placebo and ginger group regarding the intensity of these symptoms before the clinical intervention (table 5). Similarly, no statistically significant differences in serum estrogen, progesterone, FSH and LH concentrations were observed between these groups, although some variation in serum levels of these hormones was observed before the clinical intervention(Table 1).

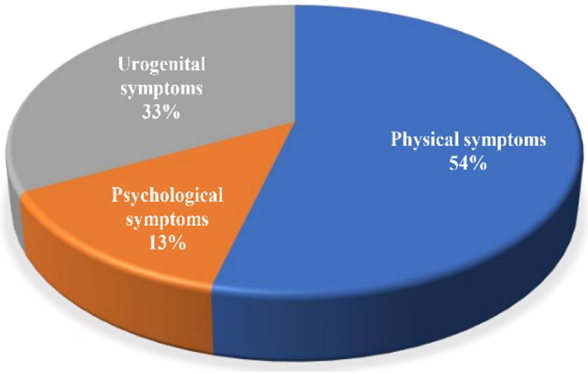


Figure 1: Prevalence of menopausal symptoms among the study participants

**Table 1:Comparison of serum female sex hormone between placebo and ginger groups at baseline**

| Medical characteristics (Pre-treatment) | Study groups Mean (SD) | | p-value (two-sided) * |
|---|---|---|---|
| | Placebo (n=20) | Ginger (n=30) | |
| **Serum Estrogen (pg/ml)** | 26.65 (12.97) | 30.94 (13.69) | 0.2741 |
| **Serum Progesterone (ng/ml)** | 0.58 (0.30) | 0.56 (0.33) | 0.863 |
| **Serum FSH (mIU/ml)** | 91.66 (5.03) | 94.10 (6.64) | 0.1722 |
| **Serum LH (mIU/ml)** | 50.64 (3.96) | 50.72 (3.46) | 0.9400 |

* An independent t-test was performed for statistical analyses. mmHg = millimeter of mercury, mIU = milli-international unit

Ginger treatment for twelve weeks significantly elevated serum estrogen levels in the treatment group as compared to the placebo group (p<0.0012), as well as to the pre-treatment ginger group (p 0.001). These results at 95% CI are shown in Table 2. However, no significant differences in serum levels of progesterone, FSH, and LH levels were found between the two groups (Table 3). Also, as depicted in Table 3, no statistically significant differences in serum progesterone and LH were reported between the pre and post-interventional ginger groups. However, treatment with ginger significantly reduced serum FSH levels in treatment group as compared to the ginger pre-treatment group (92.67 vs. 94.10; 95% CI) (p= 0.001).With respect to the effect on menopausal symptoms, ginger treatment significantly reduced these symptoms when compared to the pre-treatment group (p < 0.001) (Figure 2). Similarly, as shown in Figure 3, the intensity of symptoms was found significantly reduced by 46% in post-treatment ginger group (p<0.001). However, no such clinical response was observed in placebo treated group. Results are shown in Table 4. In addition, physical symptoms of menopause were found to be most significantly effected by ginger treatment as shown in Tables 5 and 6. A substantial reduction in

these symptoms was observed in individuals who were given ginger as compared to those in placebo ($p<0.02$) and in pre-treatment ginger group ($p<0.001$). However, significant differences were observed in psychological and urogenital symptoms between the two groups (Table 5). On the other hand, significant reduction in sexual symptoms of menopausal was found between pre and post-intervention in the ginger group ($p<0.01$) (Table 6).

**Table 2: Comparison of serum female sex hormone between placebo and ginger groups after intervention.**

| Medical characteristics (post-treatment) | Study groups Mean (SD) | | |
|---|---|---|---|
| | Placebo (n=20) | Ginger (n=30) | p-value (two-sided)* |
| **Serum Estrogen (pg/ml)** | 24.68 (10.54 | 38.02 (14.98 | **0.0012 *** |
| **Serum Progesterone (ng/ml)** | 0.44 (0.30 | 0.52 (0.32 | 0.3830 |
| **Serum FSH (mIU/ml)** | 91.99 (5.03 | 92.64 (6.56 | 0.2184 |
| **Serum LH (mIU/ml)** | 50.89 (3.83 | 51.06 (3.27 | 0.8726 |

[a] An independent t-test was performed for statistical analyses. The bold red numbers show significant differences.

**Table 3: Comparison of serum female sex hormones between ginger pre and post-intervention.**

| Medical biomarkers | Ginger Mean (SD) | | | |
|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Mean diff (95% CI) | p-value* (two-sided) |
| **Serum Estrogen (pg/ml)** | 30.94 | 38.01 | -7.08 (-9.288 to -4.87) | **0.001*** |
| **Serum Progesterone (ng/ml)** | 0.56 | 0.656 | -0.089 (-0.236 to 0.05) | 0.228 |
| **Serum FSH (mIU/ml)** | 94.10 | 92.67 | 1.416 (1.02 to 1.81) | **0.001*** |
| **Serum LH (mIU/ml)** | 50.72 | 51.06 | -0.34 (-0.34 to 0.89) | 0.3223 |

* A paired t-test was performed for statistical analyses. The bold red numbers show significant differences.

**Table 4: Comparison of MRS scores between pre and post-intervention in placebo and ginger groups.**

| | Placebo Mean (SD) | | | |
|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Mean diff (95% CI) | p-value (two-sided) |
| **MRS scoring system** | 12.35 (2.66) | 11.75 (2.44) | -0.6 (-0.40 to 1.6) | 0.225* |
| **MRS** | **No. (%)** | **No. (%)** | | |
| Asymptomatic | 7 (35 %) | 7 (35 %) | | 0.453** |
| Mild to moderate | 13 (65 %) | 13 (65 %) | | |
| | **Ginger Mean (SD)** | | | |
| **MRS scoring system** | 13.83 (2.82) | 10.50 (3.07) | -3.33 (-2.266 to -4.00) | **<0.001*** |
| **MRS** | **No. (%)** | **No. (%)** | | |
| Asymptomatic | 5 (16.67 %) | 19 (63.33 %) | | **0.001**** |
| Mild to moderate | 25 (83.33 %) | 11 (36.67 %) | | |

* paired test and ** McNemar tests were performed for statistical analyses.

**Table 5: Comparison of the menopausal symptoms between the placebo and ginger groups at baseline and after the intervention.**

| Menopausal rating scale Domain | Treatment Groups | | P-value * |
|---|---|---|---|
| | Placebo (n=20) | Ginger (n=30) | |
| | Mean (SD) | Mean (SD) | |
| **Physical symptoms pre-treatment** | 4.60 (2.01) | 5.37 ( 1.790) | 0.164 |
| **Psychological symptoms pre-treatment** | 1.23 (0.280) | 1.25 (0.371) | 0.788 |
| **Urogenital symptoms pre-treatment** | 2.85 (1.663) | 3.20 (1.270) | 0.404 |
| **Physical symptoms post-treatment** | 5.20 (1.908) | 4.03 (1.51) | **0.02** * |
| **Psychological symptoms post-treatment** | 1.20 (0.402) | 1.10 (0.359) | 0.374 |
| **Urogenital symptoms post-treatment** | 2.35 (1.56) | 2.53 (1.35) | 0.672 |

* McNemar test was performed for statistical analyses

**Table 6: Comparison of the menopausal symptoms between pre and post-intervention in placebo and ginger groups.**

| Menopausal rating scale Domain | Placebo-treated group (n=20) | | P-value * |
|---|---|---|---|
| | Pre-treatment Mean (SD) | Post-treatment Mean (SD) | |
| **Physical symptoms** | 4.60 (2.01) | 5.20 (1.908) | 0.055 |
| **Psychological symptoms** | 1.23 (0.280) | 1.20 (0.359) | 0.81 |
| **Urogenital symptoms** | 2.85 (1.663) | 2.35 (1.56) | 0.126 |
| **Ginger-treated group (n=30)** | | | |
| **Physical symptoms** | 5.37 ( 1.790) | 4.03 (1.51) | **0.001*** |
| **Psychological symptoms** | 1.25 (0.371) | 1.10 (0.402) | 0.059 |
| **Urogenital symptoms** | 3.20 (1.270) | 2.53 (1.35) | **0.01*** |

* McNemar test was performed for statistical analyses

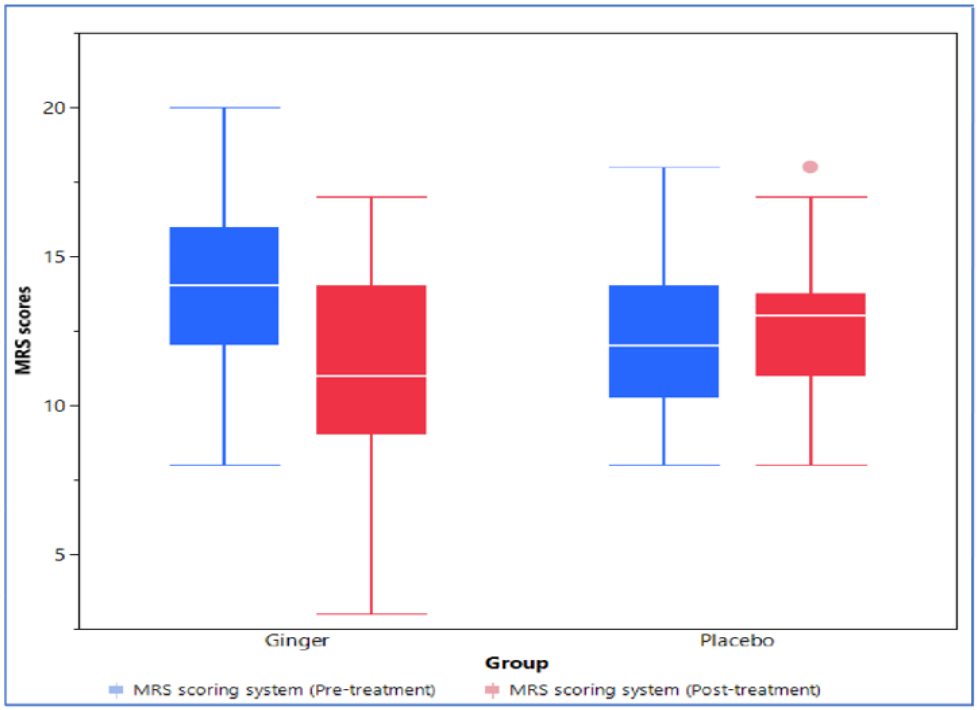


Figure 2: Comparison of MRS score between placebo and ginger groups at pre and post-treatment

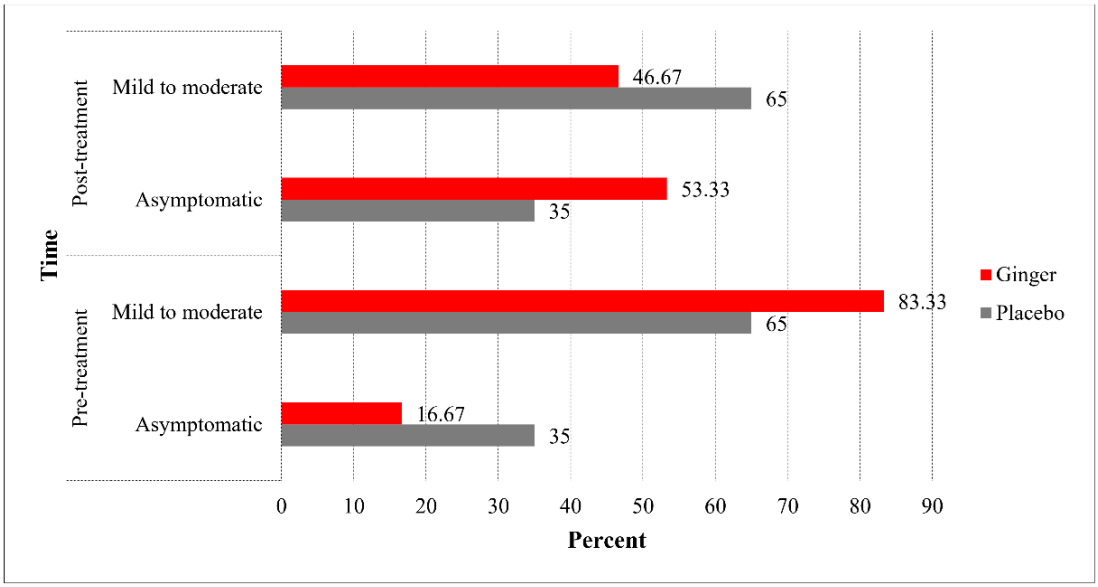


Figure 3: Comparison of incidence of quality of life between placebo and ginger groups at pre and post-treatmen

## Discussion

Menopausal problems can be divided into short-term with highly bothersome symptoms, such as hot flashes and night sweats, and long-term chronic conditions such as cognitive dysfunction, cardiovascular disease (CVD) and osteoporosis.[17] Menopausal symptoms vary according to the characteristics of individuals and their ethnicities.[18,19] For instance, a study reported hot flashes as the most common complaint by women in Basra and Erbil while in Baghdad and Mosel, joint and muscular pain was the most dominant symptom.[20-23] The current study showed that more than half of the participants suffered from physical symptoms (vasomotor symptoms and joint and muscle pain), which is in accordance with other studies in Iraq and China.[24] Another study reported physical symptoms to be the most prevalent in menopausal women.[21] The worldwide prevalence of joint and muscle pain in menopausal women is most probably related to hormonal changes during menopause. For example, fluctuation in estrogen levels during the menopausal transition has been linked to degenerative musculoskeletal diseases. In addition, these changes lead to disc degeneration and narrowing of intervertebral disc space.[25] Several studies have reported different menopausal symptom outcomes and the use of different diagnostic tools to assess these symptoms as the possible reason behind this variation.[26]

Although menopause is a physiological process, these changes are tremendous and significantly impair the quality of life of some women and need evaluation and proper treatment.[17] Various pharmacological and non-pharmacological methods of addressing these symptoms are available. Menopause hormone therapy (MHT) is the most efficient treatment method which efficiently prevent long-term estrogen deficiency. However, there is an increasing interest in complementary and alternative medicine worldwide.[27]

Ginger is one of the essential complementary medicines used to promote health and treat many diseases.[14] This study observed significant elevation of estrogen and a considerable reduction in FSH in the serum level of menopausal women who took ginger powder for three months. Similar results with estrogen and glutathione levels were observed by another study which used ginger honey.[28] Another study reported a similar elevation of estrogen levels in mice after treating them with nanoparticles lipid carriers (NLCS) loaded with gingerols.[29] Likewise, the use of alcoholic extract ginger during pregnancy and lactation in rats was found to increase the levels of sex hormones and ovarian follicles count in second-generation female rats.[30] Ginger constituents like sesquiterpenes, phenolics and diarylheptanoids exhibit estrogenic activity.[12] These derivatives are structurally analog to endogenous estradiol and have been used to treat various conditions including menopausal syndrome and osteoporosis.[31] Besides, low dose of ginger also positively affects folliculogenesis in short time.[32] Additionally, small doses of ginger have been found not only to positively affect menstrual irregularities but also to inhibit ovarian cancer cells and enhance long-term implantation in rats.[33] Moreover, some studies showed that ginger could enhance fertility index in male rats by improving serum testosterone level, testis and seminal vesicle weight, sperm motility, its count and quality also.[34,35] On the contrary, a study reported significant decrease in serum concentration of LH and estrogen hormones and an increase in serum levels of FSH and progesterone in rats treated with ginger extract.[36]

Although, the exact mechanism of how ginger increases estrogen levels is unknown, yet, some studies suggest that reducing the secretion of FSH and LH via an effect on the pituitary-gonadal axis can manage this elevation.[37] Data from the present study also support the notion that an increase in estrogen level might be associated with a reduction in FSH in blood, however, other mechanisms might probably be behind this elevation in estrogen levels in the ginger treated group.

After menopause, ovarian follicles undergo atresia with sparing of the androgen-producing theca-interstitial cell component; therefore, most estrogen in the blood comes from the aromatization of androgen in peripheral organs in males and females.[38] Intersetingly, ginger (6-gingerol) has been found to enhance aromatase activity in the peripheral tissue; thereby, elevating the estrogen levels.[38] Furthermore, ginger might increase estrogen production from a remnant of ovaries by interfering with mechanisms of ovarian aging by blocking inflammatory reactions and reducing oxidative stress.[39]

This study shows a significant reduction in physical symptoms of menopause in ginger treated group. A similar finding was reported by a study in Japan in which Kampo, a famous traditional herb containing ginger, was found to significantly lessen the postmenopausal symptoms.[40] Similar results were observed with another ginger containing plant "aphrodite" which dramatically relieved menopausal problems in Persian women. Likewise ginger constituents were reported to significantly ameliorate postmenopausal symptoms in another study.[41] Furthermore, a plant "valerian" was founf to reduce hot flashes in menopausal women compared to the placebo group. This biological effect is due to a significant amount of sesquiterpenes in this plant which is also present in ginger.[42]

The mechanism by which ginger reduces these symptoms is not known. The physiological changes in menopausal women are triggered by changes in sex hormones.[43] Therefore, some menopausal symptoms might be related to estrogen deficiency in the brain because this hormone is essential in keeping brain active and homeostasis.[44]

For example, hot flashes, which menopausal women often report, are related to estrogen deficiency in the central nervous system, which lead to narrowing of the thermoneutral zone in the brain. In addition, peripheral vascular reactivity is also altered in symptomatic women.[33] Furthermore, low doses of estrogens for eight weeks are also reported to reduce the frequency of vasomotor symptoms in menopausal women by 75% and their intensity by 87%.[45] Therefore, the role of ginger in reducing physical menopausal symptoms might be either due to increased endogenous estrogen levels or due to the direct estrogenic activity of ginger constituents on the brain.[12]

Ginger has potent anti-inflammatory and antioxidant properties[46] and turmeric, a plant from the ginger family, has also been found to reduce joint pain and tenderness and to lower cartilage degeneration.[47] This clinical effect of ginger on joint and muscular pain could be mediated by boosting estrogen production, which has a double impact on bone. First, it inhibits osteoclastogenesis while increasing intestinal and renal calcium absorption. Second, its chemical ingredients contain anti-inflammatory properties, which lower inflammatory markers.[48]

## Conclusion

This study showed that most of the menopausal women in Duhok city, Iraq, complaint about the physical symptoms than sexual and psychological symptoms. In addition, ginger powder taken orally for three months significantly reduced the frequency and intensity of vasomotor symptoms which led to a significant elevation of estrogen levels and reduction in the level of FSH in the blood.

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